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(Commemoration Issue Dedicated to
Professor Hiroshi Ibagaki, Professor Michio
Kurata, Professor Ryozo Kitamura, On the
Occasion of Their Retirements)

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CITATION:

Tseng, Yin-Chao ...[et al]. Radiopaque Materials for Embolization (Commemoration Issue Dedicated to Professor Hiroshi Ibagaki, Professor Michio Kurata, Professor Ryozo Kitamura, On the Occasion of Their Retirements). Bulletin of the Institute for Chemical Research, Kyoto University 1989, 66(3): 232-240

ISSUE DATE:

1989-02-15

URL:

<http://hdl.handle.net/2433/77238>

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Radiopaque Materials for Embolization

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Received September 5, 1988

To find a new contrast medium which provides to isobutyl cyanoacrylate (IBCA) an appropriate set time in blood, viscosity and radiopacity, new materials for therapeutic embolization have been prepared by mixing IBCA with perbromoperfluorocarbons (BPFC) at varying compositions. BPFC used in this work include hexafluorodibromopropane (FPB₂) and tetrafluorodibromoethane (FEB₂). Although mixing of conventional contrast media (lipiodol and iophendylate) with IBCA leads to an increase in the viscosity and the set time in blood, the new mixtures from BPFC reveal fairly low viscosities and quite short set times. X-ray observation shows that the 5:5 mixture of IBCA and BPFC is satisfactory with radiopacity. Furthermore, BPFC exhibits insignificant toxicity in an acute test with mice by oral administration. Consequently, the newly prepared materials seem very promising for clinical applications as radiopaque embolization materials.

KEY WORDS: Cyanoacrylate/ Embolization/ Contrast medium/ Arteriovenous malformation/

INTRODUCTION

Cerebral vascular anomalies such as cerebral arteriovenous malformations (AVM) and cerebral arteriovenous fistulas have been menaces to human life¹⁾. Surgical resection and therapeutic embolization are the only ways of treatment for these diseases. The therapeutic embolization of cerebral vascular lesions with 2-cyanoacrylates (CA), which are known as surgical adhesives, is currently a relatively common clinical procedure²⁻⁷⁾. As the anomalies can be completely embolized by deposition of CA within the nidus of the lesion, the therapeutic embolization with CA is considered as more effective treatment than that using solid embolizing substances such as silicone and spocell*, which are used as proximal occlusion of cerebral vascular anomalies.

The embolization with CA is generally carried out either by femoral approach or by craniotomy. In the former case, in which CA is injected through a balloon catheter to the nidus of lesion, a contrast medium should be added to CA which lacks in radiopacity. As CA is hydrophobic, the contrast medium should be also lipophilic so as to be dissolved in CA. In addition, the contrast medium must be stable in CA and should not interfere with polymerization of CA. Very few lipophilic contrast media are available at present. Among them are lipiodol and iophendylate. However, when they are mixed with CA, its polymerization time becomes very long and its viscosity becomes very high. Prolonged polymerization may bring about flowing-down of the

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mixture to unexpected places before complete polymerization. High viscosity of the mixture may cause breakage of the superselective catheter or uncomplete obliteration of nidus due to an insufficient amount of the embolus agent.

The present work was undertaken to study whether perbromoperfluorocarbons (BPFC) added to isobutyl cyanoacrylate (IBCA) could be new contrast media to solve all these problems.

EXPERIMENTAL

IBCA was synthesized with the conventional method from isobutyl cyanoacetate and paraformaldehyde⁸⁾. BPFC were supplied by Daikin Industries LTD., Osaka, Japan. The chemical structure and the boiling point of BPFC are given in Fig. 1. A commercial contrast medium, lipiodol ultrafluide[®] (lipiodol) was used for comparison.

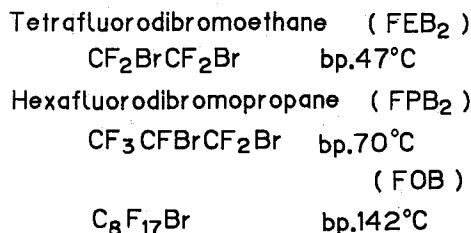


Figure 1. Chemical structure of perbromoperfluorocarbons (BPFC).

Viscosities of the mixtures of IBCA with the contrast media were measured by a rotational viscometer (Tokyo Keiki Co., LTD., Japan) at 25°C. Set times of the mixtures in blood were determined by dropping 10 μ l of the mixtures from a height of 9 mm on fresh canine blood which was placed in 41 mm Petri dish to 7 mm depth, followed by measuring the period of time just from the contacting moment of the mixtures on the blood surface to that of the complete opacification at 25°C⁹⁾. The set time was then determined by averaging fifteen readings. The set times of the mixtures in vitro were determined according to the following procedure. After the surface of stainless steel test strips (16 \times 25 \times 100 mm³) was polished with a 240 number sand paper, rinsed rigorously with acetone, and dried at 50°C for 4 hours, they were kept at 60% RH and 25°C overnight. After applying 10 μ l of the mixtures to the adhesion surface in accordance with JISK 6861-77, a weight of 5 kg was hung on the end of the bonded test strips in a certain time period, while the other end of the bonded test strips was fixed. The set time was then determined as the duration from the start until to the moment when adhesion fracture occurred. Ten measurements were made to obtain the average value. JCL-ICR mice were used for acute tests of BPFC by oral administration. Angiography of the embolus agent was carried out using mongrel dogs.

RESULTS

Solubility

Both tetrafluorodibromoethane (FEB_2) and hexafluorodibromopropane (FPB_2) were miscible with IBCA in all proportions, while the mixture of IBCA with perfluorooctylbromide (FOB) which had the highest molecular weight among BPFC, was separated into two phases within a few minutes. Therefore, the latter was not studied any more in this work.

Viscosity

The viscosities of the IBCA-BPFC mixtures as well as the IBCA-lipiodol mixtures are shown in Fig. 2. The lipiodol itself has a high viscosity such as 35 cP, while the viscosity of FEB_2 and FPB_2 is both only 2.5 cP. The viscosity of the IBCA-lipiodol mixture drastically increases with the increasing amount of the lipiodol. In contrast, the viscosity of the mixtures of IBCA with FEB_2 or FPB_2 is quite low over the whole mixing concentrations, slightly decreasing with the increasing amount of FEB_2 or FPB_2 .

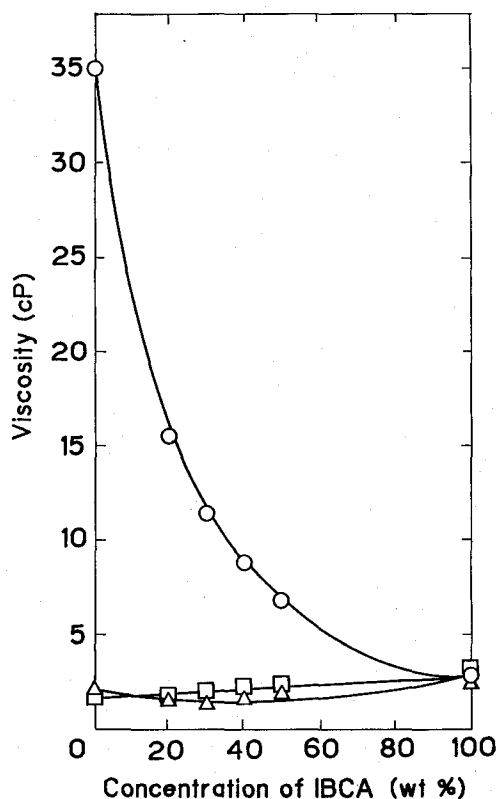


Figure 2. Viscosities of mixtures of isobutyl cyanoacrylate (IBCA) and contrast media with various compositions; (Δ) hexafluorodibromopropane, (\square) tetrafluorodibromoethane, and (\circ) lipiodol ultra-fluide.

Set time

We determined the set time of the mixtures by dropping them in blood. The reason why we chose this special method among many possible ways to determine the set time was that dropping the mixtures in blood was fairly close to the clinical application of the embolizing material. Another method with the steel test strips, which is generally used for determining the set time of instantaneous adhesives such as CA for industrial purposes, was also employed to estimate the set times of the mixtures in vitro. The set times of the mixtures of IBCA with the contrast media in blood are shown in Fig. 3. The set time of the IBCA-lipiodol mixture has a concentration dependence similar to that of the viscosity. The set time of the mixture increases steeply as the lipiodol concentration increases. The set time of the IBCA and iophendylate mixture reported by Cromwell et al.¹⁰⁾ was given in Fig. 3 for comparison. The set time change resulted upon adding iophendylate is not remarkable at least in the IBCA concentration range higher than about 30 wt%, but both BPFC (FEB₂ and FPB₂) have no effect on the polymerization of IBCA up to 80 wt% of the BPFC concentration in the mixtures.

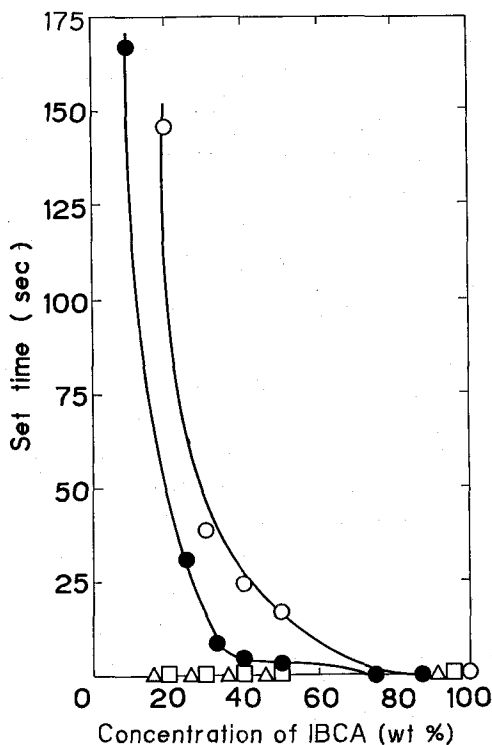


Figure 3. Set times of mixtures of isobutyl cyanoacrylate (IBCA) and contrast media (in blood) with various compositions; (△) hexafluorodibromopropane, (□) tetrafluorodibromoethane, (○) lipiodol ultra-fluide, and (●) iophendylate.

The set times of the IBCA-FPB₂ mixtures using the steel test strips are shown in Fig. 4. Interestingly, the set time of the IBCA-FPB₂ mixture increases greatly as the FPB₂ is added. This result is different from that obtained from the experiment done in blood. The reason is not clear to us at present, but it seems that the set times in blood are apparent polymerization times, while those measured with steel test strips are basically the times until to complete polymerization.

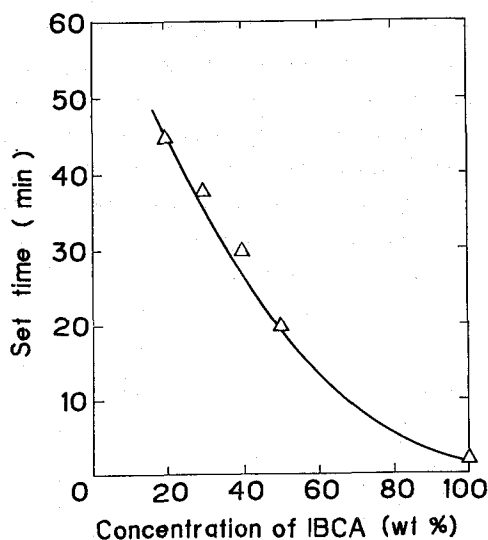


Figure 4. Set times of mixtures of isobutyl cyanoacrylate (IBCA) and hexafluoro-dibromopropane with various compositions (steel test strips).

Radiopacity

Balloon catheters filled with the mixtures of various compositions of IBCA and FPB₂ were superimposed over a normal human skull and the roentgen photograph was taken. The result is shown in Fig. 5. The ratios of IBCA to FPB₂ are 10:0, 8:2, 7:3, 6:4, and 5:5. It is seen that the best radiopacity is obtained with the 5:5 IBCA-FPB₂ mixture. In Fig. 6, the radiopacity of the mixture is compared with the 5:5 IBCA-FEB₂ mixture. As is apparent, they have almost the same radiopacity.

Toxicity

As described above, the non-radiopacity of IBCA could be solved by adding FPB₂ or FEB₂, but there is an important factor to examine before its clinical application. That is toxicity of FEB₂ and FPB₂. Thus, their acute toxicity was tested by oral administration to mice. The result is given in Table 1. The LD₅₀ of FEB₂ is found to be 0.626–2.5 g/kg and that of the FPB₂ 0.125–2.5 g/kg. The maximal administration dosage necessary for angiography is below 2–3 g/60kg and much lower than the LD₅₀ for both BPFC. It is likely that FEB₂ may be safer than FPB₂.

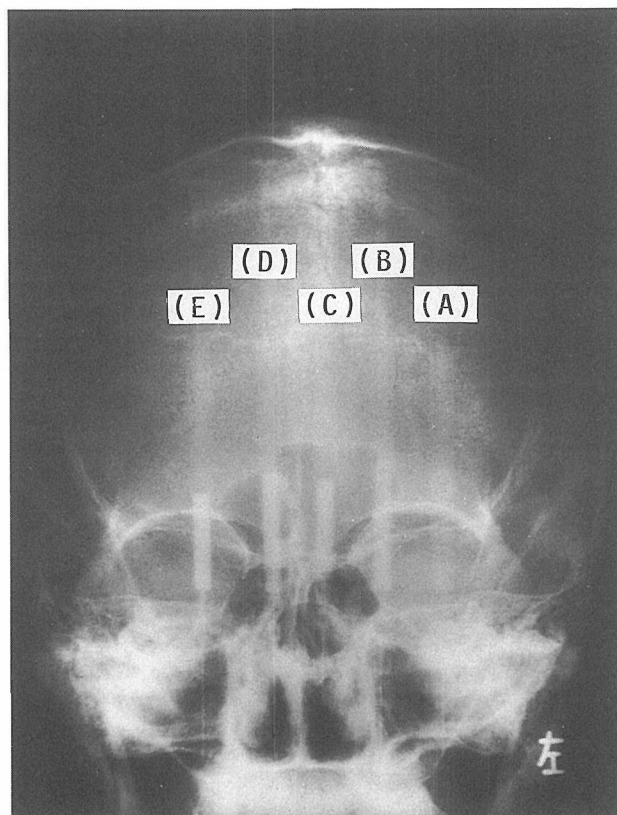


Figure 5. Catheters superimposed over normal human skull. Catheters are filled with mixtures of isobutyl cyanoacrylate and hexafluorodibromopropane with various compositions; (A) 10:0, (B) 8:2, (C) 7:3, (D) 6:4, and (E) 5:5.

Angiography

Fig. 7 shows an angiogram obtained for canine carotid artery after injecting the 5:5 IBCA-FEB₂ mixture. The mixture could be injected very easily into the artery, indicating that the mixture was able to reach even very small arteries.

DISCUSSION

The viscosity as well as the set time of embolus agents are very important physical factors for successful embolization, since they are injected into small nidus of cerebral vascular lesion and must be solidified there as quickly as possible. In addition, the embolus agents should be radiopaque, but their set time should not be altered greatly on addition of a contrast medium. When CA is employed as the quickly polymerizable liquid, the contrast medium to be added should be able to be dispersed or dissolved in the lipophilic CA without retarding the polymerization. As CA needs moisture for the rapid polymerization, a lipophilic contrast medium applicable to CA is hard to find. So

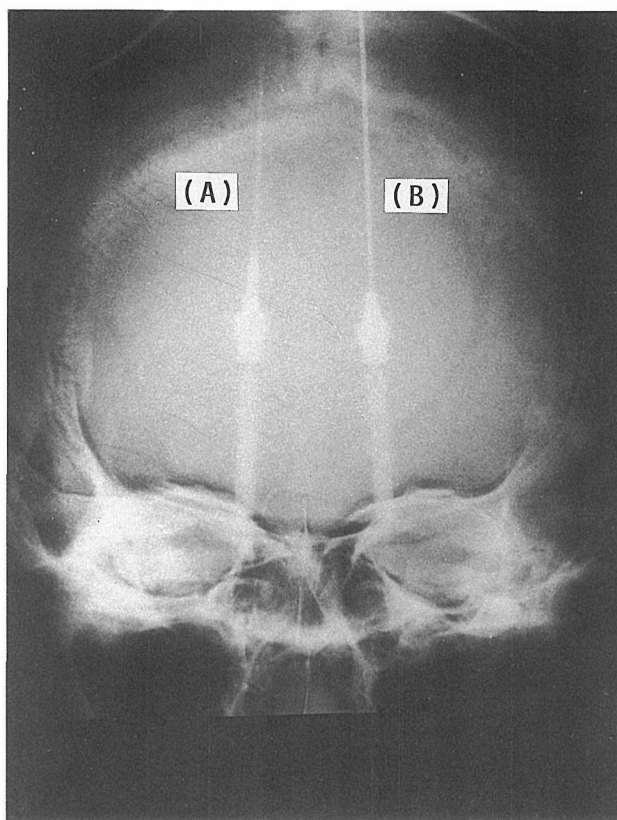


Figure 6. Catheters superimposed over normal human skull. Catheters are filled with the 5:5 mixture of isobutyl cyanoacrylate and contrast media; (A) tetrafluorodibromoethane and (B) hexafluorodibromopropane.

far, only lipiodol and iophendylate have been used as contrast medium for CA, but iophendylate at present is not commercially available in Japan any more. There are other problems for both the contrast media as described above. The viscosity of the mixtures of CA with lipiodol and iophendylate increases with the increasing amount of the contrast media. On the contrary, the new BPFC has a low viscosity and its radiopacity is satisfactory. A large quantity of embolus agent is not allowed to be injected for embolization. As there has been significant advance in computer technology and digital subtraction angiography can be performed on embolization, it is possible to reduce the content of the contrast medium in embolus agent less than 50 wt%. The set time of the BPFC-IBCA mixture is shorter than that of other mixtures. A too short set time is not desirable, because of difficulty in handling at angiography, but retarding the polymerization is much easier than accelerating it. We have not found any problem yet at least for injecting this newly developed embolus agent into canine carotid arteries.

As far as the oral administration to mice is concerned, the new embolus agent from IBCA and BPFC do not provoke any acute toxic reactions. Relatively low boiling

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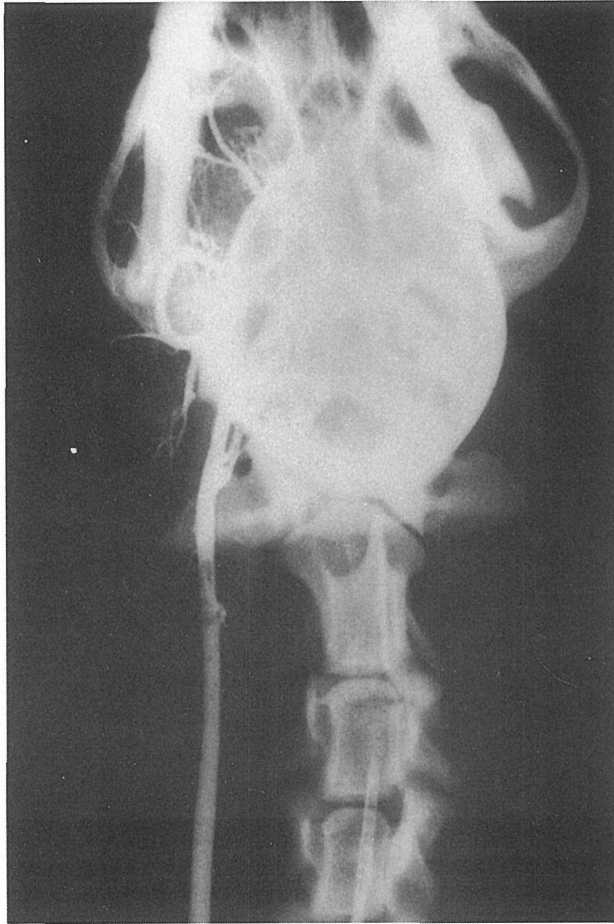


Figure 7. Angiogram of canine carotid artery after injecting the 5:5 isobutyl cyanoacrylate and tetrafluorodibromoethane mixture.

Table 1. Acute toxicity of Perbromoperfluorocarbons for JCL-ICR mice (oral administration).

	LD ₅₀	
FEB ₂	0.63~2.5	g/kg
	37.5~150	g/60kg
FPB ₂	0.13~2.5	g/kg
	7.5~30	g/60kg

points of BPFC are advantageous, because the contrast media will be rapidly excreted by exhalation. However, it is true that there must be some differences in LD₅₀ between the oral administration and the intraarterial injection. Moreover, it would be more complicated when the contrast medium is mixed with IBCA. Thus, a study for

toxicity of the embolus agents is in progress with intraarterial injection and other administration methods for dog.

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